ROLE OF TRACE ELEMENTS (ZINC, MANGANESE AND COPPER) IN THE REGULATION OF HUMAN MICROBIOTA

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ABSTRACT: The availability of vital trace elements has a significant impact on the composition and function of the human microbiota, a dynamic and tightly controlled ecosystem. As cofactors for enzymes involved in DNA synthesis, energy production, and oxidative stress defense, zinc (Zn), manganese (Mn), and copper (Cu) are essential micronutrients for microbial metabolism. However, when these metals are present in excess, they are inherently poisonous, thus both the host and the microbes must exercise rigorous regulatory control. Through homeostatic and immune-mediated processes, the host actively modifies trace element availability to limit pathogen virulence and microbial growth. This process is known as nutritional immunity. As a result, pathogenic and commensal bacteria have developed complex methods for acquiring, storing, and detoxifying metals that allow them to survive in environments that are either metal-rich or metal-restricted. Zn, Mn, and Cu homeostasis disruptions—caused by dietary imbalance, inflammation, or illness—can dramatically change microbial community structure, metabolic activity, and ecological stability, leading to dysbiosis and increased susceptibility to disease, according to growing experimental and clinical evidence. With a focus on mechanistic insights into metal-dependent microbial physiology, host-microbe competition, and their significance to health and illness, this narrative review incorporates current understanding on the roles of zinc, manganese, and copper in controlling the human microbiota. Future approaches to targeted microbiome

modification and therapeutic intervention may benefit from a better knowledge of trace element–microbiota interactions.

KEY WORDS: Human microbiota; trace elements; zinc; manganese; copper; nutritional immunity.

INTRODUCTION: The gastrointestinal system, mouth cavity, skin, urogenital tract, and other bodily regions are home to a highly varied and dynamic population of bacteria known as the human microbiota. These microbial communities play crucial functions in host physiology, contributing to nutrition metabolism, immune system modulation, barrier function, and protection against pathogens. Numerous factors, including genetics, diet, environment, and—most importantly—the availability of vital micronutrients, affect the stability and composition of the microbiota.

Trace elements including zinc (Zn), manganese (Mn), and copper (Cu) are micronutrients that are essential cofactors for a variety of microbial enzymes that control transcription, energy metabolism, DNA replication, and oxidative stress defense. However, when these metals are present in excess, they are inherently hazardous, requiring strict control by both host and microbial systems. As a result, Zn, Mn, and Cu availability and distribution become crucial factors in determining microbial growth, survival, and community structure.

Through processes for absorption, transport, storage, and excretion, the host actively maintains trace element homeostasis; this process is frequently accelerated during infection and inflammation. This control, referred to as nutritional immunity, modifies commensal bacteria populations while limiting the availability of vital metals to invasive pathogens. Proteins that sequester, redistribute, or take advantage of metals to preserve microbial homeostasis and reduce pathogen pathogenicity include calprotectin, metallothioneins, and ceruloplasmin.

In response, microorganisms have developed complex adaptations to thrive in habitats that are metal-limited or metal-toxic. These consist of efflux pumps, metal-binding proteins, enzymatic detoxification routes, and high-affinity metal transport systems. The microbiome's competitive relationships, colonization dynamics, and ecological stability are shaped by variations in these adaptive strategies among microbial taxa.

There is growing evidence that disruptions in the availability or balance of Zn, Mn, and Cu can result in major changes in the composition of microbial communities, metabolic activity, and functional resilience. These disruptions can be caused by dietary deficiencies, supplements, illness, or inflammatory conditions. Dysbiosis, weakened immunological responses, and heightened vulnerability to infections and chronic inflammatory illnesses are all linked to these changes.

The purpose of this narrative review is to summarize what is now known about the functions of copper, manganese, and zinc in controlling the human microbiota. The focus is on mechanistic insights into host-microbe competition, metal-dependent microbial physiology, and the effects of metal dysregulation on health and illness, indicating possible directions for therapeutic approaches that target the microbiome.

TRACE ELEMENTS AND MICROBIAL PHYSIOLOGY: GENERAL PRINCIPLES: Trace elements are micronutrients that are needed in very small amounts for cellular activity, but they have a significant impact on the metabolic processes of both microbial and host cells. Among them, many enzymatic reactions, electron transport mechanisms, and the structural stability of proteins depend on zinc (Zn), manganese (Mn), and copper (Cu). In contrast to macronutrients, trace elements play two roles: they are required for catalytic activity in vital pathways, but when they are present in excess, they may be cytotoxic. This duality needs finely

calibrated systems for trace element uptake, intracellular trafficking, use, and detoxification within both host and microbial cells.

Copper, manganese, and zinc all have different but related metabolic functions. An estimated 10% of microbial proteins, including those involved in protein synthesis, nucleic acid metabolism, and gene expression regulation, depend on zinc as a crucial cofactor. As a cofactor for manganese-dependent superoxide dismutases and enzymes essential to the metabolism of carbohydrates, manganese mainly contributes to the reduction of oxidative stress. As a cofactor for cytochrome c oxidase in bacterial respiratory chains and for enzymes that detoxify reactive oxygen species, copper takes part in redox processes.

Strict intracellular homeostasis is necessary due to these metals' intrinsic reactivity. Unbound Zn, Mn, or Cu can cause oxidative damage and defective proteins by catalyzing the generation of reactive oxygen species or displacing other necessary metal cofactors. For the purpose of binding, transporting, and storing metals, both hosts and bacteria use specific proteins. Together, metallochaperones, efflux pumps, metalloregulatory transcription factors, and high-affinity import systems (such as ABC transporters and NRAMP homologues) keep intracellular metal quotas within physiological ranges. These systems are not passive; in response to oxidative stress, interspecies competition, and environmental metal concentrations, their expression is dynamically regulated.

The idea of metal competition is essential to the ecological dynamics of the human microbiota. The microenvironment, which is frequently constrained by host sequestration mechanisms, must provide microorganisms with adequate trace elements. Acquisition systems that outcompete other bacteria or provide a greater affinity for ligands generated from the host provide a selection advantage in this situation. On the other hand, bacteria with ineffective detoxification or acquisition mechanisms are repressed, changing the composition of communities and their

functional potential.Concurrently, as a component of innate immunity, the host deliberately modifies trace element bioavailability. This strategy, known as nutritional immunity, entails both the relocalization of metals to infection sites where they have direct antimicrobial effects and the sequestration of vital metals by host proteins to starve potential infections. Proteins like ceruloplasmin, metallothioneins, and calprotectin are examples of this host-driven regulation that affects both commensal and pathogenic species.

Because Zn, Mn, and Cu are essential to both microbial and host biology, changes in their availability—whether brought on by changes in diet, inflammation, infection, or disease states—have a significant impact on the composition and function of microbes. Variations in trace element homeostasis can affect host physiology, encourage dysbiosis, and change competing hierarchies within the microbiota. Clarifying how trace metals control microbial ecosystems and influence health and disease requires an understanding of these mechanisms.

Comparative Analysis of Zinc, Manganese, and Copper in Human Microbiota Regulation: Despite being necessary in very small amounts, trace elements have a disproportionate impact on host and microbial biology. Although zinc (Zn), manganese (Mn), and copper (Cu) are necessary cofactors in basic metabolic processes, their reactivity can be hazardous when present in excess. Specialized mechanisms for controlling metal availability have developed in both host and microbial systems, resulting in a dynamic interplay that determines host-microbe relationships, competitive interactions, and the structure of microbial communities. The functions of Zn, Mn, and Cu in important regulatory domains are contrasted below.

Biological Roles in Microbial Physiology

Zinc (Zn): DNA and RNA polymerases, proteinases, and regulatory transcription factors are just a few of the many microbial enzymes that use zinc as a

structural and catalytic cofactor. Zn works mainly through coordination chemistry, stabilizing protein folds and facilitating catalytic activity without taking part in electron transfer, in contrast to redox-active metals. Transcriptional regulators and zinc-dependent metalloproteases are essential for bacterial metabolism and stress reactions. Additionally, zinc supports the synthesis of cell walls and membrane integrity.

Manganese (Mn): Due to its involvement in manganese-dependent superoxide dismutases (Mn-SOD), manganese plays a crucial part in the defense against oxidative stress. By catalyzing the dismutation of superoxide radicals, these enzymes shield cells from oxidative damage. Mn also aids in the processing of nucleic acids and is involved in the enzymes that metabolize carbohydrates. In microbial physiology, Mn differs from Zn and Cu due to its role as an antioxidant cofactor.

Copper (Cu): Because of its redox activity, copper can take part in electron transfer processes, which are necessary for aerobic respiration in some bacteria through cytochrome c oxidases. But because of this similar redox potential, free Cu can catalyze Fenton-like reactions, producing reactive oxygen species that harm proteins, membranes, and nucleic acids. As a result, microbial systems strike a compromise between strong detoxification mechanisms and Cu's usefulness in energy metabolism.

HOST REGULATION AND NUTRITIONAL IMMUNITY:

ZINC SEQUESTRATION: Through transporters (ZIPs, ZnTs), hosts control zinc and bind it to proteins like metallothioneins. S100 proteins, particularly calprotectin, sequester zinc in extracellular spaces during inflammation, restricting microbial access and inhibiting the proliferation of pathogens. A fundamental component of dietary immunity is the active withholding of zinc. Commensals with

high-affinity acquisition mechanisms can still obtain zinc despite suppression, influencing community dynamics.

MANGANESE RESTRICTION: By using transporters and binding proteins, the host sequesters Mn, thereby reducing its availability at mucosal surfaces. Additionally, calprotectin has a strong affinity for Mn, depriving microorganisms of this necessary cofactor, especially in inflammatory situations. Microbiota taxa's competitive outcomes are influenced by the selective pressure given by Mn restriction.

COPPER REDISTRIBUTION AND TOXICITY: By storing and concentrating Cu in phagolysosomes inside macrophages and at infection sites, the host takes use of Cu's antibacterial qualities. Cu is transported in plasma via ceruloplasmin, and cellular export is controlled by ATP7A/B. Microbial cells that are unable to efficiently detoxify or efflux Cu ions are harmed by elevated Cu concentrations at infection sites, which contribute to metal-mediated toxicity.

EFFECTS OF MICROBIOTA COMPOSITION AND DIVERSITY

ZINC DRIVEN – SHIFT: It has been demonstrated that changes in zinc availability affect the composition of gut microbes. While excessive zinc supplementation might encourage the growth of opportunistic Enterobacteriaceae, zinc deficiency is linked to a decrease in the prevalence of beneficial taxa like Bifidobacterium and Lactobacillus. These changes imply that Zn levels affect the organization of metabolic networks and microbial diversity.

MANGANESE AND COMMUNITY STABILITY: Mn affects microbial taxa's ability to withstand oxidative stress. Its restriction may lessen variety in inflammatory conditions by selectively suppressing bacteria with high Mn reliance. On the other hand, increased Mn availability could encourage the establishment of

species that have stress defense mechanisms dependent on Mn, changing the balance of competition.

COPPER AND MICROBIAL SELECTION: Microbial community rearrangement can result from Cu toxicity's suppression of vulnerable bacterial communities. Under Cu stress, several bacteria have Cu-detoxifying efflux systems (e.g., CopA, CusCFBA) that provide survival advantages. In habitats with elevated Cu levels, these adaptations may result in a greater relative abundance of Cu-resistant species.

IMPLICATIONS FOR HEALTH AND DISEASE: Zinc imbalance and dysbiosis. Increased intestinal permeability, weakened immunity, and susceptibility to infection are all correlated with zinc deficiency. Inflammatory bowel disorders and compromised mucosal immunity may be caused by dysbiotic changes linked to altered zinc bioavailability. Manganese limitation and inflammation. Mn sequestration can promote bacteria with alternate antioxidant defenses while suppressing Mn-dependent microorganisms during inflammation. The dysbiosis seen in inflammatory conditions like Crohn's disease and ulcerative colitis may be exacerbated by this selective pressure. Pathogen Suppression and Copper. Pathogen removal may be aided by host immune cells' utilization of Cu as an antibacterial. Chronic Cu increase at mucosal surfaces, however, may also reduce commensal populations, which could lead to dysbiotic conditions and compromised barrier functioning.

CLINICAL IMPLICATIONS AND TRANSLATIONAL PERSPECTIVES:

Clinical practice and translational research are significantly impacted by the interaction between trace elements—zinc (Zn), manganese (Mn), and copper (Cu)—and the human microbiome. Changes in microbial composition, community stability, host vulnerability to infection, and chronic inflammatory disorders can all

result from disruptions in metal homeostasis, whether brought on by dietary deficiencies, supplements, inflammation, or illness.

Zinc-Related Clinical Implications: Reduced microbial diversity, compromised gut barrier function, and heightened vulnerability to gastrointestinal infections are all linked to zinc deficiency. Inadequate zinc-induced dysbiosis might weaken mucosal immunity and worsen inflammatory bowel disease (IBD). On the other hand, too much zinc may encourage the growth of opportunistic diseases like Enterobacteriaceae, highlighting the need to keep zinc levels in check for microbial equilibrium. Clinical strategies that target zinc levels, such as regulated supplementation, have demonstrated promise in lowering infection rates in populations at risk of deficiency, especially in cohorts of children and the elderly.

Manganese-Related Clinical Implications: Microbial oxidative stress responses depend on manganese, and host-driven Mn sequestration during inflammation can change the dynamics of microbial communities. The persistence of dysbiotic conditions seen in chronic inflammatory illnesses may be attributed to disruption of Mn availability. Restoring microbial equilibrium and lowering the burden of inflammation may be possible using therapeutic approaches that take Mn bioavailability into account, such as dietary modification or targeted metal chelation.

Copper-Related Clinical Implications: The host uses copper's antibacterial qualities to inhibit microorganisms at infection sites. On the other hand, commensal microbial communities may unintentionally be impacted by localized Cu elevation, which could lead to dysbiosis. Clinicians might think of ways to maximize Cu's antibacterial capabilities while reducing negative effects on beneficial microbiota by taking into account its dual roles as a harmful agent and a necessary cofactor. Cu-based antimicrobial surfaces and targeted regulation of Cu homeostasis in the respiratory or gastrointestinal tract are examples of emerging translational strategies.

Integrated Metal–Microbiota Therapeutic Considerations: The comparison of Zn, Mn, and Cu shows that host health and microbial balance depend on careful control of trace element availability. Interventions must take into consideration the host immunological responses, microbial metal acquisition capacities, and the dose-dependent impacts of these metals. Personalized strategies, including customized micronutrient supplementation or microbiota-targeted treatments that alter metal availability, have the potential to improve results in the treatment of metabolic illnesses, inflammatory conditions, and infections. Furthermore, knowing how trace elements affect microbial ecology offers chances to anticipate and avoid dysbiosis, especially in susceptible groups like intensive care unit patients, malnourished people, and people with long-term inflammatory illnesses. Precision control of the microbiome to maximize host-microbe symbiosis may be possible through the integration of metal profiling with metagenomic and metabolomic investigations.

FUTURE RESEARCH DIRECTIONS: Future study will face both opportunities and problems due to the complex interactions between zinc (Zn), manganese (Mn), and copper (Cu) and the human microbiome. Even if the information currently available clarifies the basic principles of host regulation and metal-dependent microbial physiology, there are still a number of important gaps that, if filled, could improve scientific comprehension and therapeutic application.

Future Research Directions

Mechanistic and Molecular Studies

It is crucial to further understand metalloregulators, detoxification pathways, and microbial metal acquisition systems.

Species-specific metal dependencies and interactions may be revealed by high-resolution research employing metagenomics, transcriptomics, and metalloproteomics.

Host–Microbiota Interaction Mapping

examining the effects of host metal redistribution and sequestration on commensal versus pathogenic populations in vivo.

Combining microbiota profiling with spatial metal imaging may reveal site-specific dynamics, especially in the mouth cavity, stomach, and mucosal surfaces.

Clinical Correlation Studies

longitudinal research relating human disease outcomes, dysbiosis, and microbiota composition to trace element status.

studies that are population-specific and take into account changes in metal homeostasis with age, inflammatory status, and dietary preferences.

Interventional Trials

controlled experiments using metal chelation or targeted micronutrient supplementation to alter the composition of the microbiome and enhance clinical results.

In order to maximize microbiome health, combination interventions that take into account metal interactions (such as Zn-Cu balance) are evaluated.

Computational and Predictive Modeling

creation of predictive models that combine host immunity, microbial competitiveness, and trace element availability to predict microbiome responses.

Personalized approaches to microbiome modification and therapeutic interventions may be made possible by systems biology techniques.

CONCLUSION: The makeup, variety, and function of the human microbiota are largely regulated by zinc, manganese, and copper. These trace elements have a significant impact on microbial physiology and ecological balance through their functions as enzyme cofactors, mediators of oxidative stress defense, and modulators of host–microbe interactions. Microbial adaptation techniques influence resilience under metal-limited or metal-toxic settings, while host-mediated mechanisms, such as nutritional immunity and metal redistribution, produce dynamic environments that shape microbial competitiveness and survival

Changes in the availability or balance of these metals can cause dysbiosis, disturb microbial homeostasis, and affect host vulnerability to infections and chronic inflammatory illnesses. These changes can be caused by dietary deficiencies, excessive supplementing, inflammation, or illness. The careful control of trace element bioavailability is crucial for preserving microbiome stability and optimum host health, as demonstrated by a comparative study of Zn, Mn, and Cu.

There is a great deal of translational potential in a fuller comprehension of trace element-microbiota interactions. Targeted therapies to improve immune function, restore microbial balance, and prevent or treat disease may be made possible by future research combining molecular, clinical, and computational methods. In the end, utilizing the regulatory functions of Zn, Mn, and Cu offers a viable path for microbiome-informed approaches in therapeutic innovation and personalized medicine.

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